REMARKS

Upon entry of the present amendment, claims 33-43 are pending in the instant application. Claim 24, having been withdrawn from consideration by the Examiner as being drawn to a non-elected invention, and claim 26 have both been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in related applications.

The Examiner has acknowledged Applicants' election with traverse, and agreed that the members of the Markush group of pending claim 42 are sufficiently few in number and closely related that a search may be made without a serious burden. Accordingly, all claims and all the antigenic epitopes will be searched. Applicants thank the Examiner.

The Specification has been amended as described above to remove references to Figures 1 and 2 as previously objected to by the Examiner. *See*, Paper No. 13, page 2. The present amendments serve only to make the suggested changes and as previously indicated by the Examiner, they do not introduce new matter.

As described above, claim 26 has been canceled without prejudice or disclaimer. Accordingly, the Examiner's objection that claim 26 is in improper dependent form because it depends from a cancelled independent claim, has been obviated.

Claims 33, 36, 39 and 41 have been amended so as to more particularly point out and distinctly claim subject matter of the present invention. In particular, pending claims 33, 36, 39 and 41 have been amended so as to recite a conclusion that what was stated in the preamble is achieved, thereby forming complete method claims as required by the Examiner. Furthermore, claims 39 and 41 have been amended so as to no longer recite "binds specifically." Accordingly, no new matter has been introduced.

I. Rejections Under 35 U.S.C. §§ 101 and 112

A. The Examiner rejects claims 26 and 33-43, under 35 U.S.C. § 101 as allegedly not being "supported by either a specific and substantial asserted utility or a well established utility." *See*, Paper No. 13, page 3. Applicants respectfully disagree and traverse this rejection.

Preliminarily, Applicants note that presently rejected claim 26 has been canceled without prejudice or disclaimer. Accordingly, the present rejection will be addressed in so far as it is understood by Applicants to apply to remaining pending claims 33-43.

A rejection under 35 U.S.C. § 101 is improper when a person of ordinary skill in the art would find credible disclosed features or characteristics of the invention, or statements made by the applicant in the written description of the invention. *See,* M.P.E.P. §§ 2107.01(II), (III) at 2100-[29-31] (Rev. 1, Feb. 2000). In addition, an applicant need only make *one* credible assertion of utility for the claimed invention to satisfy 35 U.S.C. § 101. *See, e.g., Raytheon v. Roper,* 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown."). *See*, M.P.E.P. at 2100-29. Finding a lack of utility is also improper if a person of ordinary skill in the art would know of a use for the claimed invention at the time the application was filed. M.P.E.P. § 2107.01(II)(B) at 2100-[29-30].

Moreover, the burden is on the Examiner to establish why it is more likely than not that one of ordinary skill in the art would doubt *(i.e.,* "question") the truth of the statement of utility. M.P.E.P. § 2107.01(II)(A) at 2100-[31-32]. Thus, the Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. *Id.* The Examiner must also present countervailing facts and reasoning sufficient to establish that a person of ordinary skill

would not believe the applicants' assertion of utility. *See id.*; *see also*, *In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). For the reasons set forth below, the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

The Examiner finds Applicants' assertions of utility to be unconvincing. In rejecting the instant claims, the Examiner states:

> because the specification has not provided any evidence that neutrokine-α or APRIL are differentially expressed in Sjogren's disease (or any disease listed), and presents an extensive list of diseases or disorders that may be diagnosed using the TR18 polypeptides, the method of detecting Sjogren's disease is not a specific or substantial utility. There is no nexus between differential expression of neutrokine-α or APRIL and Sjogren's disease. . . . . The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides.

See, Paper No. 13, pages 4-5.

Preliminarily, Applicants contend that the provision of a number of specific utilities in the specification is proper. Indeed, the M.P.E.P. states:

> It is common and sensible for an applicant to identify several specific utilities for an invention, ... an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility.

See, M.P.E.P. § 2107.02.I at 2100-37. Accordingly, the Examiner's apparent determination that an asserted utility is not specific or substantial simply because it is not the sole assertion of utility, is improper.

Furthermore, although the Examiner did not explicitly raise the issue of credibility, Applicants assert that the asserted utility is also credible. Applicants respectfully point out, that expression levels of Neutrokine-alpha <u>have</u> been shown to be elevated in

Sjögren's disease. As Applicants demonstrate below, it is clear that those of skill in the relevant art believe that Neutrokine-alpha levels are diagnostic of Sjögren's disease.

Preliminarily, Applicants respectfully point out that the names Neutrokine-alpha, BLyS and BAFF, all serve to identify the same polypeptide molecule. Enclosed herewith please find copies of Shu et al., GenBank database accession No. NP_006564, and Ebner et al., Geneseq database accession No. AAW58391, identified as Exhibits A and B respectively. Examination of the amino acid sequence of BLyS/BAFF, as disclosed in Exhibit A, confirms that it shares 100% sequence identity with the amino acid sequence of Neutrokine-alpha as disclosed in Exhibit B.

Applicants direct the Examiner's attention to Groom et al., *J. Clin. Invest.* (2002) 109:59-68, and to Mariette et al., *Ann. Rheum. Dis.* (2003) 62:168-171. Legible copies of Groom et al., and Mariette et al., are enclosed herewith as Exhibits C and D respectively. Individually and together, these references demonstrate that elevated Neutrokine-alpha (referred to as BLyS or BAFF in the references) levels are found in the serum of patients with Sjögren's Syndrome.

Groom et al states, in the left column of page 60:

> ...we tested sera from patients with SS [Sjögren's syndrome], and demonstrated levels of circulating BAFF that were significantly elevated compared with levels in healthy control individuals;

and they conclude, in the right column of page 67:

> ...[t]hese results support the idea that an imbalance in BAFF production could be a major factor contributing to the development of SS.

Independently of the findings of Groom et al., Mariette et al. confirmed that elevated levels of Neutrokine-alpha are found in the serum of patients with Sjögren's

disease, and that such levels are correlated to the levels of autoantibodies diagnostic for the disease. Mariette et al. state, in the left column of page 168:

> [w]e have assessed BLyS levels in serum from patients with primary SS and shown a correlation between the level of BLyS and both the level of immunoglobulins and the titre of autoantibodies.

These reports demonstrate that Neutrokine-alpha levels are elevated in patients with Sjögren's disease and it is clear from statements made in these publications that the authors believe that Neutrokine-alpha levels are a good indicator, *i.e.*, diagnostic marker, of Sjögren's disease. Accordingly, Applicants contend that the instant application asserts a credible utility for the present invention, *i.e.*, the detection of Sjögren's disease, and fulfills the requirements of 35 U.S.C. § 101.

Once more, Applicants respectfully submit that TR18 of the invention (such as, for example, the polynucleotide shown as SEQ ID NO:1), has an immediate and specific utility. Such polynucleotide may be used to detect Sjögren's disease. Thus, polypeptides of the invention are supported by an immediate utility that is both specific and substantial.

In summary, the asserted utility for TR18 is specific (not every protein may be used to detect Sjögren's disease) and substantial ("the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6)). In addition, these utilities are credible. The Examiner has failed, however, to provide any countervailing statements as to why these particular utilities are not specific, substantial and credible.

Even assuming, *arguendo,* the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by proffering sufficient evidence to lead one skilled in the art to conclude that the asserted utilities are more likely than not true.

In view of the above, Applicants submit that the asserted utilities of the invention meet the statutory requirement set forth in 35 U.S.C. § 101. The Examiner has failed to establish and maintain grounds as to why a rejection for lack of utility is proper. Accordingly, Applicants respectfully request that the rejection of claims 33-43 under 35 U.S.C. § 101 be withdrawn.

B. The Examiner has also rejected claims 26 and 33-43 under 35 U.S.C. § 112, first paragraph, as allegedly not being "supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention". *See*, Paper No. 13, Page 5. Applicants respectfully traverse this rejection and assert that each of the claims pending prior to and after the present amendment is fully supported and satisfies the statutory enablement requirements under 35 U.S.C. § 112.

As detailed above, the asserted utilities of the invention meet the statutory requirement set forth in 35 U.S.C. § 101 and, armed with the specification of the instant invention, one skilled in the art clearly would know how to use the claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 33-43 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

C. The Examiner has also rejected claims 41-43 under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to provide enablement "commensurate in scope with the claims." *See*, Paper No. 13, pages 5-6.

Applicants respectfully point out that claim 41, and claims dependent therefrom, have been amended to no longer recite "an isolated polypeptide comprising an antigenic epitope of the amino acid sequence of SEQ ID NO:2." Therefore, rejection of the instant

claims based on the supposed use of any protein "comprising any 4 amino acids of the sequence of SEQ ID NO:2" in the claimed method is obviated.

Accordingly, Applicants respectfully request that the rejection of claims 41-43 under 35 U.S.C. § 112, first paragraph, for lack of enablement, be reconsidered and withdrawn.

D. The Examiner has also rejected claims 26 and 33-43 under 35 U.S.C. § 112, second paragraph, as allegedly failing "to particularly point out and distinctly claim the subject matter which applicants regard as the invention." *See*, Paper No. 13, Page 6. Applicants respectfully traverse this rejection and assert that each of the claims pending prior to and after the present amendment is fully supported and satisfies the statutory requirements of 35 U.S.C. § 112.

Preliminarily, Applicants note that presently rejected claim 26 has been canceled without prejudice or disclaimer. Accordingly, the present rejection will be addressed in so far as it is understood by Applicants to apply to remaining pending claims 33-43.

Claims 39 and 41, and claims dependent therefrom, have been amended to no longer recite "specifically." Accordingly, rejection of the instant claims based on the recitation of "binds specifically" is obviated.

Claims 33, 36, 39 and 41 have been rewritten with the method steps clearly recited. Accordingly, rejection of the instant claims based on the improper recitation of method steps is obviated.

Accordingly, Applicants respectfully request that the rejection of claims 33-43 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Conclusion

Applicants respectfully request consideration and entry of the foregoing remarks into the file. Applicants believe that no fee is due in connection herewith; however, should the Patent Office determine otherwise, please charge the required fee to Human Genome Sciences, Inc., Deposit Account No. 08-3425.

Respectfully submitted,

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Enclosures
KKH/JMM/BM

VIA HAND DELIVERY MARCH 17TH, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: RUBEN et al.

Application Serial No.: 09/848,271 Art Unit: 1646

Filed: May 4, 2001 Examiner: O'Hara, E.

For: Human Tumor Necrosis Factor TR18 and Methods Based Thereon Attorney Docket No.: PF526N

VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Specification:

At page 4, line 17, the entire paragraph beginning "[t]he present invention provides," has been replaced by the following amended paragraph:

--The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding at least a portion of TR18. Thus, the present invention provides, for example, isolated nucleic acid molecules comprising a polynucleotide encoding the TR18 receptor having the amino acid sequence shown in ~~Figure 1~~ (SEQ ID NO:2~~)~~.--

At page 6, line 19, the entire section entitled "Brief Description of the Figures" has been deleted.

At page 7, line 15, the entire paragraph beginning "[t]he present invention provides" has been replaced by the following amended paragraph:

--The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding TR18, such as, for example, polynucleotides having the nucleotide sequence shown in ~~Figure 1~~ (SEQ ID NO:1~~)~~. The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding a TR18 polypeptide having the amino acid sequence shown in ~~Figure 1~~ (SEQ ID NO:2~~)~~.--

At page 7, line 22, the entire paragraph beginning "[t]he determined nucleotide sequence" has been replaced by the following amended paragraph:

--The determined nucleotide sequence of TR18 (~~Figure 1;~~ SEQ ID NO:1) contains an open reading frame encoding a protein of about 184 amino acid residues, with a deduced molecular weight of about 20.1 kDa. The amino acid sequence of the predicted mature TR18 receptor is shown in SEQ ID NO:2 from amino acid residue about 1 to residue about 184.--

At page 8, line 5, the entire paragraph beginning "[t]he present invention provides" has been replaced by the following amended paragraph:

--The present invention provides a nucleotide sequence encoding the mature TR18 polypeptide having the amino acid sequence shown in ~~Figure 1~~SEQ ID NO:2. By the mature TR18 protein having the amino acid sequence shown in ~~Figure 1~~SEQ ID NO:2 is meant the mature form(s) of the TR18 receptor predicted by computer analysis or produced by expression of the coding sequence shown in ~~Figure 1~~SEQ ID NO:2 in a mammalian cell (e.g., COS cells, as described below). As indicated below, the mature TR18 receptor having the amino acid sequence encoded by the coding sequence shown in ~~Figure 1~~SEQ ID NO:2 may or may not differ from the predicted mature TR18 protein shown in ~~Figure 1~~SEQ ID NO:2 (amino acids from about 1 to about 184) depending on the accuracy of the predicted cleavage site based on computer analysis.--

At page 8, line 21, the entire paragraph beginning "[t]he polypeptide sequence" has been replaced by the following amended paragraph:

--The polypeptide sequence of the TR18 depicted in ~~Figure 1~~SEQ ID NO:2 can routinely be examined by computer programs. For example, the mature form, intracellular form, extracellular form, and transmembrane domains of the TR18 polypeptides of the invention can routinely be predicted via analysis using the "PSORT" computer program (K. Nakai and M. Kanehisa, *Genomics* 14:897-911 (1992)), which is an expert system for predicting the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated into the PSORT program.--

At page 8, line 29, the entire paragraph beginning "[t]he predicted TR18 polypeptide," and extending onto page 9, has been replaced by the following amended paragraph:

--The predicted TR18 polypeptide comprises about 184 amino acids. However, as one of ordinary skill in the art would appreciate, the actual TR18 polypeptide may be anywhere in the range of 174-194 amino acids due to the possibilities of sequencing errors as well as the variability of cleavage sites for leaders in different known proteins. It will further be appreciated that, the domains described herein have been predicted by computer analysis, and accordingly, that depending on the analytical criteria used for identifying various functional domains, the exact "address" of, for example, the extracellular domain, intracellular domain, cysteine-rich motif, and transmembrane domain of TR18 may differ slightly from the predicted locations. For example, the exact location of the TR18 extracellular domain in ~~Figure 1 (~~SEQ ID NO:2~~)~~ may vary slightly (e.g., the address may "shift" by about 1 to about 20 residues, more likely about 1 to about 5 residues) depending on the criteria used to define the domain. In any event, as discussed in more detail below, the invention further provides polypeptides having various residues deleted from the N-terminus and/or C-terminus of the complete TR18 polypeptide, including polypeptides lacking one or more amino acids from the N-termini of the TR18 extracellular domains described herein, which constitute soluble forms of the extracellular domain of the TR18 polypeptides respectively.--

At page 10, line 3, the entire paragraph beginning "[i]solated nucleic acid molecules," has been replaced by the following amended paragraph:

--Isolated nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) shown in ~~Figure 1 (~~SEQ ID NO:1~~)~~; DNA molecules comprising the coding sequence for the complete (full-length) and/or mature TR18 protein shown in ~~Figure 1 (~~SEQ ID NO:2~~)~~; and DNA molecules which comprise a sequence substantially different from those described above, but which, due to the degeneracy of the genetic code, still encode the TR18 protein. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.--

At page 10, line 11, the entire paragraph beginning "[t]he invention further provides," has been replaced by the following amended paragraph:

--The invention further provides an isolated nucleic acid molecule having the nucleotide sequence shown in ~~Figure 1~~ (SEQ ID NO:1~~)~~, or a nucleic acid molecule having a sequence complementary thereto. Such isolated molecules, particularly DNA molecules, are useful, for example, as probes for gene mapping by *in situ* hybridization with chromosomes, and for detecting expression of the TR18 gene in human tissue, for instance, by Northern blot analysis.--

At page 10, line 17, the entire paragraph beginning "[t]he present invention is further," and extending onto page 11, has been replaced by the following amended paragraph:

--The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated DNA molecule having the nucleotide sequence of the nucleotide sequence shown in ~~Figure 1~~ (SEQ ID NO:1~~)~~ is intended DNA fragments at least about 15 nt, and more preferably at least about 20 nt, at least about 24 nt, still more preferably at least about 30 nt, at least about 35 nt, and even more preferably, at least about 40 nt, at least about 45 nt, at least about 50 nt, at least about 55 nt, at least about 60 nt, at least about 65 nt, at least about 70 nt, at least about 75 nt, at least about 100 nt, at least about 150 nt, at least about 200 nt, at least about 250 nt, at least about 300 nt in length which are useful, for example, as diagnostic probes and primers as discussed herein. Of course, larger fragments 350-833 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence as shown in ~~Figure 1~~ (SEQ ID NO:1~~)~~, or the complementary strand thereto. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of the nucleotide sequence as shown in ~~Figure 1~~ (SEQ ID NO:1~~)~~. In this context "about" includes the particularly recited size, and sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In specific embodiments, the fragments of the invention comprise, or alternatively consist of, nucleotides 91-105, 148 to 159, 211 to 222, 379 to 399, 463 to 492, 543

to 564 of ~~Figure 1~~ (SEQ ID NO:1~~)~~ or the complementary strand thereto. Polypeptides encoded by these polynucleotide are also encompassed.--

At page 11, line 6, the entire paragraph beginning "[r]epresentative examples," has been replaced by the following amended paragraph:

--Representative examples of TR18 polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to 33, 34 to 66, 67 to 87, 88 to 120, 121 to 156, 157 to 189, 190 to 228, 229 to 255, 256 to 282, 283 to 306, 307 to 336, 337 to 369, 370 to 399, 400 to 432, 433 to 462, 463 to 495, 496 to 525, 526 to 558, 559 to 588, 589 to 618, 619 to 648, 649 to 678, 679 to 711, 712 to 741, 742 to 771, 772 to 804, and/or 805 to 834 of ~~Figure 1~~ (SEQ ID NO:1~~)~~, or the complementary strand thereto. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.--

At page 11, line 15, the entire paragraph beginning "[i]n specific embodiments," has been replaced by the following amended paragraph:

--In specific embodiments, the polynucleotide fragments of the invention comprise, or alternatively, consist of, a sequence from nucleotide 88 to 189, of ~~Figure 1~~ (SEQ ID NO:1~~)~~, or the complementary strand thereto.--

At page 12, line 31, the entire paragraph beginning "[p]referred nucleic acid fragments," and extending onto page 13, has been replaced by the following amended paragraph:

--Preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding a member selected from the group: a polypeptide comprising or alternatively, consisting of, the TR18 receptor extracellular domain (amino acid residues from about 1 to about 54 in ~~Figure 1~~ (SEQ ID NO:2~~)~~; a polypeptide comprising, or alternatively consisting of, the TR18 cysteine rich domain (amino acid residues from about 8 to about 41 in ~~Figure 1~~ (SEQ ID NO:2~~)~~; a polypeptide comprising, or alternatively consisting of the TR18 transmembrane domain (amino acid residues from about 55 to about 80 in ~~Figure 1~~ (SEQ ID NO:2~~)~~; and/or a polypeptide comprising, or alternatively consisting of, the TR18 intracellular

domain (amino acid residues from about 81 to about 184 in ~~Figure 1 (~~SEQ ID NO:2~~)~~). Since the locations of these domains have been predicted by computer analysis, one of ordinary skill would appreciate that the amino acid residues constituting these domains may vary slightly (e.g., by about 1 to 15 amino acid residues) depending on the criteria used to define each domain.--

At page 13, line 13, the entire paragraph beginning "[p]referred nucleic acid fragments of the invention," has been replaced by the following amended paragraph:

--Preferred nucleic acid fragments of the invention encode a full-length TR18 polypeptide lacking the nucleotides encoding the amino terminal methionine in ~~Figure 1 (~~SEQ ID NO:1~~)~~, as it is known that the methionine is cleaved naturally and such sequences may be useful in genetically engineering TR18 expression vectors. Polypeptides encoded by such polynucleotides are also contemplated by the invention.--

At page 13, line 18, the entire paragraph beginning "[p]referred nucleic acid fragments of the present invention," and extending onto page 14, has been replaced by the following amended paragraph:

--Preferred nucleic acid fragments of the present invention further include nucleic acid molecules encoding epitope-bearing portions of the TR18 receptor proteins. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising amino acid residues from about 9 to about 13 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; a polypeptide comprising amino acid residues from about 28 to about 31 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; a polypeptide comprising amino acid residues from about 49 to about 52 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; a polypeptide comprising amino acid residues from about 105 to about 111 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; a polypeptide comprising amino acid residues from about 133 to about 142 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; and a polypeptide comprising amino acid residues from about 160 to about 166 in ~~Figure 1 (~~SEQ ID NO:2~~)~~. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. The inventors have determined that the above polypeptide fragments are antigenic regions of the TR18 proteins. Methods for determining other such epitope-bearing portions of the TR18 proteins are described in detail below.--

At page 14, line 2, the entire paragraph beginning "[i]t is believed," has been replaced by the following amended paragraph:

--It is believed that the extracellular cysteine rich motifs of TR18 disclosed in ~~Figure 1~~SEQ ID NO:2 are important for interactions between TR18 and its ligands (e.g., Neutrokine alpha and APRIL). Accordingly, specific embodiments of the invention are directed to polynucleotides encoding polypeptides which comprise, or alternatively consist of, the amino acid sequence of amino acid residues 8 to 41 of ~~Figure 1~~ (SEQ ID NO:2). Polypeptides encoded by these polynucleotides are also encompassed by the invention..--

At page 14, line 15, the entire paragraph beginning "[t]he data representing," has been replaced by the following amended paragraph:

--The data representing the structural or functional attributes of TR18 set forth in ~~Figure 2 and/or~~ Table I, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, XI, XIII and XIV of Table I can be used to determine regions of TR18 which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, XI, XIII and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.--

At page 14, line 24, the entire paragraph beginning "[c]ertain preferred regions," has been replaced by the following amended paragraph:

--Certain preferred regions in these regards ~~are set out in Figure 2, but~~ may~~,~~ ~~as shown in Table I,~~ be represented or identified by using tabular representations of the data presented in ~~Figure 2~~Table I. The DNA*STAR computer algorithm used to generate ~~Figure 2~~Table I (set on the original default parameters) was used to present the data ~~in Figure 2~~ in a tabular format (See Table I). The tabular format of the data ~~in Figure 2~~ may be used to easily determine specific boundaries of a preferred region.--

At page 14, line 30, the entire paragraph beginning "[t]he above-mentioned preferred regions," and extending onto page 15, has been replaced by the following amended paragraph:

--The above-mentioned preferred regions set out in ~~Figure 2 and in~~ Table I, include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequences set out in ~~Figure 1~~SEQ ID NO:2. As set out in ~~Figure 2 and in~~ Table I, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Hopp-Woods hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions.--

At page 18, line 25, the entire paragraph beginning "[b]y a polynucleotide which hybridizes," has been replaced by the following amended paragraph:

--By a polynucleotide which hybridizes to a "portion" of a polynucleotide is intended a polynucleotide (either DNA or RNA) hybridizing to at least about 15 nucleotides (nt), and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably about 30-70 nt of the reference polynucleotide. These are useful, for example, as diagnostic probes and primers as discussed above and in more detail below. By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., the nucleotide sequence as shown in ~~Figure 1~~ (SEQ ID NO:1~~)~~. In this context "about" includes the particularly recited size, and sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.--

At page 19, line 1, the entire paragraph beginning "[i]n further embodiments," has been replaced by the following amended paragraph:

--In further embodiments, polynucleotides of the invention comprise at least 15, at least 30, at least 50, at least 100, or at least 250, at least 500, or at least 800 contiguous nucleotides of TR18 coding sequence, but consist of less than or equal to 100 kb, 75 kb, 50 kb, 30 kb, 25 kb, 20 kb, 15 kb, 10 kb, or 5 kb of genomic DNA that flanks the 5' or 3' coding nucleotide set forth in ~~Figure 1~~ (SEQ ID

NO:1~~)~~. In further embodiments, polynucleotides of the invention comprise at least 15, at least 30, at least 50, at least 100, or at least 250, at least 500, or at least 800 contiguous nucleotides of TR18 and/or coding sequence, but do not comprise all or a portion of any TR18 intron. In another embodiment, the nucleic acid comprising TR18 coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the TR18 gene in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).--

At page 20, line 15, the entire paragraph beginning "[f]urther embodiments of the invention," has been replaced by the following amended paragraph:

--Further embodiments of the invention include isolated nucleic acid molecules comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence at least 80%, 85%, or 90% identical, and more preferably at least 95%, 96%, 97%, 98%, or 99% identical to: (a) a nucleotide sequence encoding the polypeptide having the amino acid sequence shown in ~~Figure 1 (~~SEQ ID NO:2~~)~~; (b) a nucleotide sequence encoding the polypeptide having the amino acid sequence in ~~Figure 1 (~~SEQ ID NO: 2~~)~~, but lacking the amino terminal methionine; (c) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions 1 to 184 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; (d) a nucleotide sequence encoding the TR18 extracellular domain; (e) a nucleotide sequence encoding the TR18 rich motif (i.e., amino acid residues 8 to 41 in ~~Figure 1 (~~SEQ ID NO:2~~))~~); (f) a nucleotide sequence encoding the TR18 transmembrane domain; (g) a nucleotide sequence encoding the TR18 receptor intracellular domain; (h) a nucleotide sequence encoding the TR18 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; and (i) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), or (h) above. Polypeptides encoded by these polynucleotides are also encompassed by the invention.--

At page 20, line 31, the entire paragraph beginning "[b]y a polynucleotide having," and extending onto page 21, has been replaced by the following amended paragraph:

--By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a TR18 polypeptide is

intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five mismatches per each 100 nucleotides of the reference nucleotide sequence encoding the TR18 polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mismatches of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The reference (query) sequence may be the entire TR18 encoding nucleotide sequence shown in ~~Figure 1 (~~SEQ ID NO:1~~)~~, or any TR18 polynucleotide fragment (e.g., a polynucleotide encoding the amino acid sequence of any of the TR18 N- and/or C-terminal deletions described herein), variant, derivative or analog, as described herein.--

At page 21, line 17, the entire paragraph beginning "[a]s a practical matter," has been replaced by the following amended paragraph:

--As a practical matter, whether any particular nucleic acid molecule is at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the nucleotide sequence shown in ~~Figure 1 (~~SEQ ID NO:1~~)~~ can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics 2*: 482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of

the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed. --

At page 23, line 3, the entire paragraph beginning "[t]he present application," has been replaced by the following amended paragraph:

--The present application is directed to nucleic acid molecules comprising, or alternatively consisting of a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequence for example, shown in ~~Figure 1 (~~SEQ ID NO:1~~)~~, irrespective of whether they encode a polypeptide having TR18 receptor activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having TR18 functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having TR18 receptor activity include, *inter alia:* (1) isolating the TR18 gene or allelic variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the TR18 receptor gene, as described in Verma *et al., Human Chromosomes: A Manual of Basic Techniques*, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting TR18 receptor mRNA expression in specific tissues.--

At page 23, line 17, the entire paragraph beginning "[p]referred, however," has been replaced by the following amended paragraph:

--Preferred, however, are nucleic acid molecules comprising, or alternatively consisting of, a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to for example, the nucleic acid sequence shown in ~~Figure 1 (~~SEQ ID NO:1~~)~~, which do, in fact, encode a polypeptide having TR18 functional activity. By "a polypeptide having TR18 functional activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of the TR18 receptor of the invention (either the full-length protein or, preferably, the mature protein), as measured in a particular biological assay.--

At page 23, line 24, the entire paragraph beginning "[o]f course, due to the degeneracy," and extending onto page 24, has been replaced by the following amended paragraph:

--Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to, for example, the nucleic acid shown in ~~Figure 1 (~~SEQ ID NO:1~~)~~, will encode a polypeptide "having TR18-short functional activity." Similarly, a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to, for example, a nucleic acid sequence shown in ~~Figure 1~~SEQ ID NO:1 will encode a polypeptide "having TR18 functional activity." In fact, since degenerate variants of these nucleotide sequences all encode the same polypeptide, this will be clear to the skilled artisan even without performing a biological assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having TR18 functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).--

At page 43, line 25, the entire paragraph beginning "[m]ultimers of the invention," and extending onto page 44, has been replaced by the following amended paragraph:

--Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when proteins of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when proteins of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the TR18 proteins of the invention. Such covalent associations

may involve one or more amino acid residues contained in the polypeptide sequence of the protein (e.g., the polypeptide sequence shown in ~~Figure 1 (~~SEQ ID NO:2~~)~~ or a polypeptide encoded by one of the deposited cDNA clones). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences of the proteins which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a TR18 fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a TR18-Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequences from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more TR18 polypeptides of the invention are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple TR18 polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.--

At page 46, line 27, the entire paragraph beginning "[a]ccordingly, in one embodiment," and extending onto page 47, has been replaced by the following amended paragraph:

--Accordingly, in one embodiment, the invention provides an isolated TR18 polypeptide having the amino acid sequence encoded by the amino acid sequence in ~~Figure 1 (~~SEQ ID NO:2~~)~~, or a polypeptide comprising, or alternatively consisting of, a portion of the above polypeptides, such as for example, a mature TR18, the TR18 extracellular domain (amino acids 1 to 54 of ~~Figure 1 (~~SEQ ID

NO:2)), the TR18 cysteine rich motif (amino acids 8 to 41 of ~~Figure 1~~ (SEQ ID NO:2)), and/or the TR18 intracellular domain (amino acids 81 to 184 of ~~Figure 1~~ (SEQ ID NO:2)).--

At page 47, line 3, the entire paragraph beginning "[p]olypeptide fragments of the present invention," has been replaced by the following amended paragraph:

--Polypeptide fragments of the present invention include polypeptides comprising or alternatively, consisting of: an amino acid sequence contained in ~~Figure 1~~ (SEQ ID NO:2); and encoded by a nucleic acid which hybridizes (e.g., under stringent hybridization conditions) to the complementary strand of the nucleotide sequence shown in ~~Figure 1~~ (SEQ ID NO:1), or a fragment thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 47, line 9, the entire paragraph beginning "[p]rotein fragments may be," has been replaced by the following amended paragraph:

--Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise or alternatively, consist of about amino acid residues: 1 to 7, 8 to 41, 41 to 54, 55 to 80, 81 to 104, 105 to 135, 136 to 165, and/or 166 to 184, of SEQ ID NO:2 ~~or Figure 1~~. In this context "about" includes the particularly recited ranges, ranges larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 or amino acids in length. Polynucleotides encoding these polypeptides are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 47, line 20, the entire paragraph beginning "[i]n additional embodiments," and extending onto page 48, has been replaced by the following amended paragraph:

--In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist of, one or more TR18 domains. Preferred polypeptide fragments of the present invention include one, two, three or more members selected from the group: (a) a polypeptide comprising or alternatively, consisting

of, the TR18 extracellular domain (predicted to constitute amino acid residues 1 to 54 ~~Figure 1~~ (SEQ ID NO:2)); (b) a polypeptide comprising or alternatively, consisting of, the TR18 cysteine rich domain (predicted to constitute amino acid residues 8 to 41 ~~Figure 1~~ (SEQ ID NO:2)); (c) a polypeptide comprising or alternatively, consisting of, the TR18 transmembrane domain (predicted to constitute amino acid residues 55 to 80 ~~Figure 1~~ (SEQ ID NO:2)); (d) a polypeptide comprising or alternatively, consisting of, the TR18 intracellular domain (predicted to constitute amino acid residues 81 to 184 ~~Figure 1~~ (SEQ ID NO:2)); (e) a polypeptide comprising, or alternatively, consisting of, one, two, three, four or more, epitope bearing portions of the TR18 protein; or (f) any combination of polypeptides (a)-(e). Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 48, line 3, the entire paragraph beginning "[a]s discussed above," has been replaced by the following amended paragraph:

--As discussed above, it is believed that the extracellular cysteine rich motif of TR18 is important for interactions between TR18 and its ligands (e.g., Neutrokine-alpha and APRIL). Accordingly, in preferred embodiments, polypeptides of the invention comprise, or alternatively consist of amino acid residues 8 to 41 of ~~Figure 1~~ (SEQ ID NO:2). Proteins comprising or alternatively consisting of a polypeptide sequence which is at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the polypeptide sequences of the cysteine rich motif are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 48, line 11, the entire paragraph beginning "[a]mong the especially preferred," has been replaced by the following amended paragraph:

--Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of TR18. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high

antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of complete (i.e., full-length) TR18 (~~Figure 1~~ (SEQ ID NO:2~~)~~). Certain preferred regions are those set out in ~~Figure 2 and~~ Table 1 and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in ~~Figure 1~~ (SEQ ID NO:2~~)~~, such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle predicted hydrophilic; Hopp-Woods predicted hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 49, line 15, the entire paragraph beginning "[a]ccordingly, the present invention," has been replaced by the following amended paragraph:

--Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the TR18 amino acid sequence shown in ~~Figure 1~~SEQ ID NO:2, up to the lysine residue at position number 179 and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-184 of ~~Figure 1~~SEQ ID NO:2, where n^1 is an integer from 2 to 179 corresponding to the position of the amino acid residue in ~~Figure 1~~ (SEQ ID NO:2~~)~~.--

At page 49, line 22, the entire paragraph beginning "[m]ore in particular," and extending onto page 50, has been replaced by the following amended paragraph:

--More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: L-2 to R-184; Q-3 to R-184; M-4 to R-184; A-5 to R-184; G-6 to R-184; Q-7 to R-184; C-8 to R-184; S-9 to R-184; Q-10 to R-184; N-11 to R-184; E-12 to R-184; Y-13 to R-184; F-14 to R-184; D-15 to R-184; S-16 to R-184; L-17 to R-184; L-18 to R-184; H-19 to R-184; A-20 to R-184; C-21 to R-184; I-22 to R-184; P-23 to R-184;

C-24 to R-184; Q-25 to R-184; L-26 to R-184; R-27 to R-184; C-28 to R-184; S-29 to R-184; S-30 to R-184; N-31 to R-184; T-32 to R-184; P-33 to R-184; P-34 to R-184; L-35 to R-184; T-36 to R-184; C-37 to R-184; Q-38 to R-184; R-39 to R-184; Y-40 to R-184; C-41 to R-184; N-42 to R-184; A-43 to R-184; S-44 to R-184; V-45 to R-184; T-46 to R-184; N-47 to R-184; S-48 to R-184; V-49 to R-184; K-50 to R-184; G-51 to R-184; T-52 to R-184; N-53 to R-184; A-54 to R-184; I-55 to R-184; L-56 to R-184; W-57 to R-184; T-58 to R-184; C-59 to R-184; L-60 to R-184; G-61 to R-184; L-62 to R-184; S-63 to R-184; L-64 to R-184; I-65 to R-184; I-66 to R-184; S-67 to R-184; L-68 to R-184; A-69 to R-184; V-70 to R-184; F-71 to R-184; V-72 to R-184; L-73 to R-184; M-74 to R-184; F-75 to R-184; L-76 to R-184; L-77 to R-184; R-78 to R-184; K-79 to R-184; I-80 to R-184; S-81 to R-184; S-82 to R-184; E-83 to R-184; P-84 to R-184; L-85 to R-184; K-86 to R-184; D-87 to R-184; E-88 to R-184; F-89 to R-184; K-90 to R-184; N-91 to R-184; T-92 to R-184; G-93 to R-184; S-94 to R-184; G-95 to R-184; L-96 to R-184; L-97 to R-184; G-98 to R-184; M-99 to R-184; A-100 to R-184; N-101 to R-184; I-102 to R-184; D-103 to R-184; L-104 to R-184; E-105 to R-184; K-106 to R-184; S-107 to R-184; R-108 to R-184; T-109 to R-184; G-110 to R-184; D-111 to R-184; E-112 to R-184; I-113 to R-184; I-114 to R-184; L-115 to R-184; P-116 to R-184; R-117 to R-184; G-118 to R-184; L-119 to R-184; E-120 to R-184; Y-121 to R-184; T-122 to R-184; V-123 to R-184; E-124 to R-184; E-125 to R-184; C-126 to R-184; T-127 to R-184; C-128 to R-184; E-129 to R-184; D-130 to R-184; C-131 to R-184; I-132 to R-184; K-133 to R-184; S-134 to R-184; K-135 to R-184; P-136 to R-184; K-137 to R-184; V-138 to R-184; D-139 to R-184; S-140 to R-184; D-141 to R-184; H-142 to R-184; C-143 to R-184; F-144 to R-184; P-145 to R-184; L-146 to R-184; P-147 to R-184; A-148 to R-184; M-149 to R-184; E-150 to R-184; E-151 to R-184; G-152 to R-184; A-153 to R-184; T-154 to R-184; I-155 to R-184; L-156 to R-184; V-157 to R-184; T-158 to R-184; T-159 to R-184; K-160 to R-184; T-161 to R-184; N-162 to R-184; D-163 to R-184; Y-164 to R-184; C-165 to R-184; K-166 to R-184; S-167 to R-184; L-168 to R-184; P-169 to R-184; A-170 to R-184; A-171 to R-184; L-172 to R-184; S-173 to R-184; A-174 to R-184; T-175 to R-184; E-176 to R-184; I-177 to R-184; E-178 to R-184; and/or K-179 to R-184 of the TR18 sequence shown in ~~Figure 1~~SEQ ID NO:2. Polypeptides encoded by these polynucleotides are also encompassed by the invention.--

At page 50, line 26, the entire paragraph beginning "[i]n another embodiment," and extending onto page 51, has been replaced by the following amended paragraph:

--In another embodiment, N-terminal deletions of the TR18 polypeptide can be described by the general formula n^2-54, where n^2 is a number from 2 to 50, corresponding to the position of amino acid identified in ~~Figure 1~~ (SEQ ID NO:2~~)~~. Preferably, N-terminal deletions of the TR18 polypeptide of the invention shown as ~~Figure 1~~ (SEQ ID NO:2~~)~~ include polynucleotides encoding polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues L-2 to A-54; Q-3 to A-54; M-4 to A-54; A-5 to A-54; G-6 to A-54; Q-7 to A-54; C-8 to A-54; S-9 to A-54; Q-10 to A-54; N-11 to A-54; E-12 to A-54; Y-13 to A-54; F-14 to A-54; D-15 to A-54; S-16 to A-54; L-17 to A-54; L-18 to A-54; H-19 to A-54; A-20 to A-54; C-21 to A-54; I-22 to A-54; P-23 to A-54; C-24 to A-54; Q-25 to A-54; L-26 to A-54; R-27 to A-54; C-28 to A-54; S-29 to A-54; S-30 to A-54; N-31 to A-54; T-32 to A-54; P-33 to A-54; P-34 to A-54; L-35 to A-54; T-36 to A-54; C-37 to A-54; Q-38 to A-54; R-39 to A-54; Y-40 to A-54; C-41 to A-54; N-42 to A-54; A-43 to A-54; S-44 to A-54; V-45 to A-54; T-46 to A-54; N-47 to A-54; S-48 to A-54; and/or V-49 to A-54 of the TR18 extracellular domain sequence shown in ~~Figure 1~~ (SEQ ID NO:2~~)~~. Polypeptides encoded by these polynucleotides are also encompassed by the invention.--

At page 51, line 10, the entire paragraph beginning "[i]n a most preferred embodiment," has been replaced by the following amended paragraph:

--In a most preferred embodiment, the polypeptides of the invention comprise, or alternatively consist of amino acids M-4 to S-44 as shown in ~~Figure 1~~ (SEQ ID NO:2~~)~~. Polypeptides at least 90%, at least 95%, at least 96%, at least 97%, and/or at least 99% identical to amino acids M-4 to S-44 as shown as ~~Figure 1~~(SEQ ID NO:2~~)~~ are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 51, line 16, the entire paragraph beginning "[i]n another most preferred embodiment," has been replaced by the following amended paragraph:

--In another most preferred embodiment, the polypeptides of the invention comprise, or alternatively consist of amino acids M-4 to T-52 as shown in ~~Figure 1~~(SEQ ID NO:2~~)~~. Polypeptides at least 90%, at least 95%, at least 96%, at least

97%, and/or at least 99% identical to amino acids M-4 to T-52 as shown as ~~Figure 1~~(SEQ ID NO:2~~)~~ are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 51, line 22, the entire paragraph beginning "[i]n another most preferred embodiment," has been replaced by the following amended paragraph:

--In another most preferred embodiment, the polypeptides of the invention comprise, or alternatively consist of amino acids M-4 to A-54 as shown in ~~Figure 1~~(SEQ ID NO:2~~)~~. Polypeptides at least 90%, at least 95%, at least 96%, at least 97%, and/or at least 99% identical to amino acids M-4 to A-54 as shown as ~~Figure 1~~(SEQ ID NO:2~~)~~ are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 52, line 10, the entire paragraph beginning "[a]ccordingly, the present invention," has been replaced by the following amended paragraph:

--Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the TR18 polypeptide shown in ~~Figure 1~~SEQ ID NO:2, up to the glycine residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising the amino acid sequence of residues 1-m^1 of ~~Figure 1~~SEQ ID NO:2, where m^1 is an integer from 6 to 183 corresponding to the position of the amino acid residue in ~~Figure 1~~ (SEQ ID NO:2~~)~~.--

At page 52, line 17, the entire paragraph beginning "[m]ore in particular," and extending onto page 53, has been replaced by the following amended paragraph:

--More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: M-1 to A-183; M-1 to S-182; M-1 to I-181; M-1 to S-180; M-1 to K-179; M-1 to E-178; M-1 to I-177; M-1 to E-176; M-1 to T-175; M-1 to A-174; M-1 to S-173; M-1 to L-172; M-1 to A-171; M-1 to A-170; M-1 to P-169; M-1 to L-168; M-1 to S-167; M-1 to K-166; M-1 to C-165; M-1 to Y-164; M-1 to D-163; M-1 to N-162; M-1 to T-161; M-1 to K-160; M-1 to T-159; M-1 to T-158; M-1 to V-157; M-1 to L-156; M-1 to I-155; M-1 to T-154; M-1 to A-153; M-1 to G-152; M-1 to E-151;

M-1 to E-150; M-1 to M-149; M-1 to A-148; M-1 to P-147; M-1 to L-146; M-1 to P-145; M-1 to F-144; M-1 to C-143; M-1 to H-142; M-1 to D-141; M-1 to S-140; M-1 to D-139; M-1 to V-138; M-1 to K-137; M-1 to P-136; M-1 to K-135; M-1 to S-134; M-1 to K-133; M-1 to I-132; M-1 to C-131; M-1 to D-130; M-1 to E-129; M-1 to C-128; M-1 to T-127; M-1 to C-126; M-1 to E-125; M-1 to E-124; M-1 to V-123; M-1 to T-122; M-1 to Y-121; M-1 to E-120; M-1 to L-119; M-1 to G-118; M-1 to R-117; M-1 to P-116; M-1 to L-115; M-1 to I-114; M-1 to I-113; M-1 to E-112; M-1 to D-111; M-1 to G-110; M-1 to T-109; M-1 to R-108; M-1 to S-107; M-1 to K-106; M-1 to E-105; M-1 to L-104; M-1 to D-103; M-1 to I-102; M-1 to N-101; M-1 to A-100; M-1 to M-99; M-1 to G-98; M-1 to L-97; M-1 to L-96; M-1 to G-95; M-1 to S-94; M-1 to G-93; M-1 to T-92; M-1 to N-91; M-1 to K-90; M-1 to F-89; M-1 to E-88; M-1 to D-87; M-1 to K-86; M-1 to L-85; M-1 to P-84; M-1 to E-83; M-1 to S-82; M-1 to S-81; M-1 to I-80; M-1 to K-79; M-1 to R-78; M-1 to L-77; M-1 to L-76; M-1 to F-75; M-1 to M-74; M-1 to L-73; M-1 to V-72; M-1 to F-71; M-1 to V-70; M-1 to A-69; M-1 to L-68; M-1 to S-67; M-1 to I-66; M-1 to I-65; M-1 to L-64; M-1 to S-63; M-1 to L-62; M-1 to G-61; M-1 to L-60; M-1 to C-59; M-1 to T-58; M-1 to W-57; M-1 to L-56; M-1 to I-55; M-1 to A-54; M-1 to N-53; M-1 to T-52; M-1 to G-51; M-1 to K-50; M-1 to V-49; M-1 to S-48; M-1 to N-47; M-1 to T-46; M-1 to V-45; M-1 to S-44; M-1 to A-43; M-1 to N-42; M-1 to C-41; M-1 to Y-40; M-1 to R-39; M-1 to Q-38; M-1 to C-37; M-1 to T-36; M-1 to L-35; M-1 to P-34; M-1 to P-33; M-1 to T-32; M-1 to N-31; M-1 to S-30; M-1 to S-29; M-1 to C-28; M-1 to R-27; M-1 to L-26; M-1 to Q-25; M-1 to C-24; M-1 to P-23; M-1 to I-22; M-1 to C-21; M-1 to A-20; M-1 to H-19; M-1 to L-18; M-1 to L-17; M-1 to S-16; M-1 to D-15; M-1 to F-14; M-1 to Y-13; M-1 to E-12; M-1 to N-11; M-1 to Q-10; M-1 to S-9; M-1 to C-8; M-1 to Q-7; and/or M-1 to G-6 of the TR18 sequence shown in ~~Figure 1~~SEQ ID NO:2. Polypeptides encoded by these polynucleotides are also encompassed by the invention.--

At page 53, line 17, the entire paragraph beginning "[t]he invention also provides," has been replaced by the following amended paragraph:

--The invention also provides polynucleotides encoding polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n^1-m^1 and/or n^2-m^1 of ~~Figure 1 (i.e.,~~

SEQ ID NO:2), where n^1, n^2, and m^1 are integers as described above. Thus, any of the above listed N- or C-terminal deletions can be combined to produce a polynucleotide encoding an N- and C-terminal deleted TR18 polypeptide.--

At page 53, line 23, the entire paragraph beginning "[i]n a most preferred embodiment," has been replaced by the following amended paragraph:

--In a most preferred embodiment, the polypeptides of the invention comprise, or alternatively consist of amino acids M-4 to S-44, or M-4 to T-52, M-4 to A-54, as shown in ~~Figure 1~~(SEQ ID NO:2). Polypeptides at least 90%, at least 95%, at least 96%, at least 97%, and/or at least 99% identical to amino acids M-4 to S-44, or M-4 to T-52, M-4 to A-54, as shown in ~~Figure 1~~ (SEQ ID NO:2) are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 53, line 29, the entire paragraph beginning "[t]he present invention encompasses," and extending onto page 54, has been replaced by the following amended paragraph:

--The present invention encompasses TR18 polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of ~~Figure 1~~ (SEQ ID NO:2), or an epitope of a polypeptide sequence encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:1 (e.g., under stringent hybridization conditions or lower stringency hybridization conditions as defined herein). The present invention further encompasses polynucleotide sequences encoding an epitope of a TR18 polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:2), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand (e.g., under stringent hybridization conditions or lower stringency hybridization conditions defined herein).--

At page 55, line 13, the entire paragraph beginning "[n]on-limiting examples," and extending onto page 56, has been replaced by the following amended paragraph:

--Non-limiting examples of antigenic polypeptides of the invention include one, two, three, four, five, or more members selected from the group: a polypeptide

comprising, or alternatively consisting of, amino acid residues from about Ser-9 to about Tyr-13 in ~~Figures 1~~ (SEQ ID NO:2); a polypeptide comprising, or alternatively consisting of, amino acid residues from about Cys-28 to about Asn-31 in ~~Figure 1~~ (SEQ ID NO:2); a polypeptide comprising, or alternatively consisting of, amino acid residues from about Val-49 to about Thr-52 in ~~Figure 1~~ (SEQ ID NO:2); a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-105 to Asp-111 in ~~Figure 1~~ (SEQ ID NO:2); a polypeptide comprising, or alternatively consisting of, amino acid residues from about Lys-133 to about His-142 in ~~Figure 1~~ (SEQ ID NO:2); and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Lys-160 to Lys-166 in ~~Figure 1~~ (SEQ ID NO:2). In this context, "about" means the particularly recited ranges and ranges that are larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the TR18 polypeptide by the analysis of the Jameson-Wolf antigenic index, as shown in ~~Figure 1 and~~ Table I, above. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)). Polynucleotides encoding these polypeptides are encompassed by the invention. Additionally, antibodies that bind to one or more of these polypeptides are also encompassed by the invention.--

At page 58, line 12, the entire paragraph beginning "[a]dditional fusion proteins," has been replaced by the following amended paragraph:

--Additional fusion proteins of the invention may be generated through the techniques of gene shuffling, motif shuffling, exon shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods

can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of TR18 polynucleotides corresponding to ~~Figure 1~~ (SEQ ID NO:1~~)~~ and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.--

At page 59, line 10, the entire paragraph beginning "[t]hus, the fragment," has been replaced by the following amended paragraph:

--Thus, the fragment, derivative, or analog of the polypeptide of ~~Figure 1~~ (SEQ ID NO:2~~)~~, may be (i) one in which at least one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue(s), and more preferably at least one but less than ten conserved amino acid residues) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence

which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein. --

At page 60, line 14, the entire paragraph beginning "[i]n specific embodiments," has been replaced by the following amended paragraph:

--In specific embodiments, the number of substitutions, additions or deletions in the amino acid sequence of ~~Figure 1~~SEQ ID NO:2 and/or any of the polypeptide fragments described herein (e.g., the cysteine rich motif, the extracellular domain and/or intracellular domain) is 75, 70, 60, 50, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 30-20, 20-15, 20-10, 15-10, 10-1, 5-10, 1-5, 1-3 or 1-2.--

At page 69, line 10, the entire paragraph beginning "[t]he polypeptide of the present invention," has been replaced by the following amended paragraph:

--The polypeptides of the present invention include a polypeptide comprising, or alternatively, consisting of: amino acids 1 to 184 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; amino acids 2 to 184 in ~~Figure 1 (~~SEQ ID NO:2~~)~~; the TR18 extracellular domain; the TR18 cysteine rich motif; the TR18 transmembrane domain; the intracellular domain of TR18; and the TR18 extracellular domain and the TR18 intracellular domain with all or part of the transmembrane domain deleted; as well as polypeptides which are at least 80% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98%, 99% or 100% identical to the polypeptides described above (e.g., the polypeptide of ~~Figure 1 (~~SEQ ID NO:2~~)~~), and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 or at least 100 amino acids. Polynucleotides encoding these polypeptides are also encompassed by the invention.--

At page 70, line 3, the entire paragraph beginning "[a]s a practical matter," has been replaced by the following amended paragraph:

--As a practical matter, whether any particular polypeptide is at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to, for instance, the amino acid sequence shown in ~~Figure 1 (~~SEQ ID NO:2~~)~~, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University

Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.--

At page 71, line 21, the entire paragraph beginning "[i]n additional embodiments," has been replaced by the following amended paragraph:

--In additional embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, 99% or 100% identical to the polynucleotide sequence encoding the extracellular cysteine rich motif of TR18 disclosed in ~~Figure 1~~SEQ ID NO:2 (amino acid residues from 8 to 41). In another embodiment, the invention provides an isolated nucleic acid molecule comprising a polynucleotide that hybridizes under stringent hybridization conditions to DNA complementary to the polynucleotide sequence encoding the TR18 extracellular cysteine rich motif. The present invention also encompasses the above polynucleotide/nucleic acid sequences fused to a heterologous polynucleotide sequence. Polypeptides encoded by these nucleic acids and/or polynucleotide sequences are also encompassed by the invention.--

At page 75, line 14, the entire paragraph beginning "[a]ntibodies of the present invention," has been replaced by the following amended paragraph:

--Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables ~~and Figures~~. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.--

At page 220, line 22, the entire paragraph beginning "[o]ligonucleotides that are complementary," and extending onto page 221, has been replaced by the following amended paragraph:

--Oligonucleotides that are complementary to the 5' end of the message, *e.g.*, the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non-translated, non-coding regions of TR18 shown in ~~Figure 1~~SEQ ID NO:1, respectively, could be used in an antisense approach to inhibit translation of endogenous TR18 mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of TR18 mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.--

At page 222, line 23, the entire paragraph beginning "[p]otential antagonists," and extending onto page 223, has been replaced by the following amended paragraph:

--Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequence can be used to destroy TR18 mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988).

There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence TR18 (~~Figure 1~~SEQ ID NO:1). Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the TR18 mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.--

At page 224, line 3, the entire paragraph beginning "[i]n other embodiments," has been replaced by the following amended paragraph:

--In other embodiments, antagonists according to the present invention include soluble forms of TR18 (e.g., fragments of TR18 shown in ~~Figure 1~~ (SEQ ID NO:2) that include one or more copies of the cysteine rich motif from the extracellular domain of TR18). Such soluble forms of the TR18, which may be naturally occurring or synthetic, antagonize TR18 mediated signaling by competing with native TR18 for binding to Neutrokine-alpha (See, U.S. Application Serial No. 60/188,208), and/or by forming a multimer that may or may not be capable of binding the receptor, but which is incapable of inducing signal transduction. Preferably, these antagonists inhibit TR18 mediated stimulation of lymphocyte (e.g., B-cell) proliferation, differentiation, and/or activation. Antagonists of the present invention also include antibodies specific for TNFR-family receptors and TR18-Fc fusion proteins.--

At page 224, line 26, the entire paragraph beginning "[a]ntagonists of the present invention," and extending onto page 225, has been replaced by the following amended paragraph:

--Antagonists of the present invention also include antibodies specific for TNF-family ligands or the TR18 polypeptides of the invention. Antibodies according to the present invention may be prepared by any of a variety of standard methods using TR18 immunogens of the present invention. As indicated, such TR18 immunogens include the complete TR18 polypeptides depicted in ~~Figure 1~~ (SEQ ID NO:2) and TR18 polypeptide fragments comprising, for example, the cysteine rich domain, extracellular domain, transmembrane domain, and/or intracellular domain, or any combination thereof.--

In the Claims:

Claims 24 and 26 have been canceled without prejudice or disclaimer.

Claims 33, 36, 39 and 41 have been replaced by the following rewritten claims:

33. (Once Amended) A method of detecting Sjögren's disease comprising, contacting an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 with a biological sample and assaying for binding of neutrokine-α to said isolated polypeptide, wherein altered binding of neutrokine-α indicates the presence of Sjögren's disease.

36. (Once Amended) A method of detecting Sjögren's disease comprising, contacting an isolated polypeptide comprising amino acids 4 to 45 of SEQ ID NO:2 with a biological sample and assaying for binding of neutrokine-α to said isolated polypeptide, wherein altered binding of neutrokine-α indicates the presence of Sjögren's disease.

39. (Once Amended) A method of detecting Sjögren's disease comprising, contacting an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 with a biological sample and assaying for binding of an antibody that ~~specifically~~ binds to said isolated polypeptide, wherein altered antibody binding indicates the presence of Sjögren's disease.

41. (Once Amended) A method of detecting Sjögren's disease comprising, contacting an isolated ~~polypeptide comprising an~~ antigenic epitope of the amino acid sequence of SEQ ID NO:2 with a biological sample and assaying for binding of an antibody that binds ~~specifically~~ to ~~said~~ an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein altered antibody binding indicates the presence of Sjögren's disease.